CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

FENOXAPROP-ETHYL

Chemical Code # 2311, Tolerance # 51910
SB 950 # New A. I.

Original: 12/22/92
Revised : 2/18/94

I. DATA GAP STATUS

Combined, rat	No data gap; no adverse effect
Chronic toxicity, dog:	No data gap; no adverse effect
Oncogenicity, rat:	See Combined, rat
Oncogenicity, mouse:	No data gap; no adverse effect
Reproduction, rat:	No data gap; no adverse effect
Teratology, rat:	No data gap; no adverse effect
Teratology, rabbit:	No data gap; no adverse effect
Gene mutation:	No data gap; no adverse effect
Chromosome effects:	No data gap; no adverse effect
DNA damage:	No data gap; no adverse effect
Neurotoxicity:	Not required for this compound at this time

Toxicology one-liners are attached.

All record numbers through #121153 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T930308

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

** 015, 016; 114456, 114457; "Combined Chronic Toxicity and Carcinogenicity Study in Rats (24 and 28 month feeding studies)" (Kramer et. al., Hoechst Aktiengesellschaft, Frankfurt, Germany, Study # 688, 6/28/85); this study represents another segment of a 24 month chronic feeding study in rats (document 51910-014, -015, record #s 114454 and 114455); 835; HOE 33171 OH AT 206 or HOE 33171 OH AS 201 (both are TGAI); 0 (diet), 5, 30, and 180 ppm to 60 rats/sex/dose for 28 months; **no adverse effects:** no treatment-related changes in mortality, body weight, food consumption, hematological parameters, and urinalysis detected; lowering of serum cholesterol (78.3% of control, $p<0.05$) and total lipids (75.8% of control, $p<0.05$) reported in high dose males; induction of hepatic enzymes in high dose animals at 12 months with reduced relative liver weight in mid- and high-dose males (88.7% of control, $p<0.05$); was not considered to be toxicologically significant without any abnormal findings in histology or hepatic function test at 24 months; distension of zona reticularis and the medulla of the adrenals and hyperplastic epithelia of the renal pelvis with calcareous deposits at 24 months was also detected; age-related dystrophy of sciatic nerve and femoral muscle were reported in control and treated animals; no oncogenic potential demonstrated with chronic feeding; NOEL (M/F) = 30 ppm (based on serum levels of cholesterol and total lipids, induction of hepatic enzymes, histological changes in the adrenals and kidneys; **acceptable**; (Leung, 11/5/92).

CHRONIC TOXICITY, RAT

** 014, 015; 114454, 114455; "Chronic Feeding Study (24 months) in Rats", (Kramer, et. al., Hoechst Aktiengesellschaft, Frankfurt, Germany, Study # 688, 9/19/84); 831; HOE 33171 OH AT 206 or HOE 33171 OH AS 201 (both are TGAI); 0 (diet), 5, 30, and 180 ppm (males: 0, 0.26, 1.58, and 9.43 mg/kg, respectively; females: 0, 0.33, 2.00, and 11.87 mg/kg, respectively); 20 rats/sex/dose; 6 rats/sex/dose for BSP/PSP function test and another 10 rats/sex/dose used for monitoring residues in organs and tissues; mortalities: males 1/20, 7/20, 2/20, 3/20; females 7/20, 7/20, 7/20, 6/20, respectively; **no adverse effect;** no treatment-related changes in body weight, food consumption, hematological parameters, urinalysis, and clinical chemistry were detected; levels of residues found in organs and tissues from the treated animals were dose-related but there was no sex differences or time-related accumulation of residues; reduction in absolute (88.7% of control, $p\leq 0.05$) and relative (89.8% of control, $p\leq 0.05$) liver weight in high dose males was not considered to be toxicologically significant in the absence of any abnormal histological changes; hepatic (BSP) and renal (PSP) tests did not reveal any functional disturbances due to HOE 33171; NOEL (M/F) = 30 ppm (males: 1.58 mg/kg, females: 2.00 mg/kg, based on induction of hepatic enzymes, changes in liver weights, distension of the zona reticularis and the medulla of the adrenals, hyperplastic epithelia of the renal pelvis with calcareous deposits); **acceptable**; (Leung, 10/30/92).

012; 114452; "Chronic Feeding Study in Rats (Interim Killing after 6 months)" (Kramer et. al., Hoechst Aktiengesellschaft, Frankfurt, Germany, Study # 688, 1/10/83); HOE 33171 OH AS 201 or HOE 33171 OH AT 206 (both are TGAI); 0(diet), 5, 30, and 180 ppm; 10 rats/sex/dose; one low dose male rat died during week 3 due to hemorrhage of the urinary bladder; all other animals survived until scheduled termination; **no adverse effects indicated;** high dose males exhibited increased body weight (110% of control, $p<0.05$) without any changes in food consumption; rats from the 180 ppm group showed partially hyperplastic epithelia of the renal pelvis with calcareous deposits (10/20 vs. 6/20 in 180 ppm and control group, respectively); **supplemental**; (Leung, 10/22/92).

013; 114453; "Chronic Feeding Study in Rats (Interim Killing After 12 Months)" (Kramer et. al., Hoechst Aktiengesellschaft, Frankfurt, Germany, Study # 688, 11/11/83); HOE 33171 OH AS 201 or HOE 33171 OH AT 206 (Both are TGAI); 0 (diet), 5, 30, and 180 ppm; 10 rats/sex/dose; all animals survived the study until scheduled termination; **no adverse effects indicated**; no treatment-related changes in behavior, clinical signs, body weight, food consumption, hematological parameters, and urinalysis were detected; elevated aminopyrine N-demethylase activity (223.5% of control, $p\leq0.05$) in high dose females and carnitine acetyltransferase activity (403.1 - 537.9% of control, $p \leq 0.05$) in high dose animals; histological exam revealed distension of the zona reticularis and medulla of the adrenals in high dose animals in the absence of discernible tissue lesions; **supplemental**; (Leung, 10/26/92).

CHRONIC TOXICITY, DOG

** 018, 065; 114458, 121144; "Toxicological Testing of HOE 33171 by Repeated Oral Administration to Beagle Dogs for 2 Years" Brunk et. al.,(Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # 85.0073, 1/30/85); 831; HOE 33171 OH ZC94 0001 (94% purity); 0 (cornmeal), 3, 15, and 75 ppm (males: 0, 0.20, 1.10, and 5.2 mg/kg, respectively; females: 0, 0.18, 0.90, and 4.60 mg/kg, respectively) to 6 dogs/sex/dose for 2 years; all animals survived the study until scheduled termination; no adverse effects; high dose females and males demonstrated reduced body weight gain (49.1 and 54.6% of control, $p<0.05$, respectively) without any abnormal changes in food consumption; no treatment-related changes in clinical signs, ophthalmological findings, hematological parameters, clinical chemistry, and urinalysis were detected; hepatic (BSP) and renal (PSP) function tests did not reveal any organ dysfunction; NOEL (M/F) = 15 ppm (males: 1.1 mg/kg, females: 0.9 mg/kg, reduced body weight gain);study originally reviewed as unacceptable but possibly upgradeable with analysis of test diet to confirm the actual concentrations of HOE 33171 employed; (Leung, 11/4/92); study was rereviewed with test diet analysis; **acceptable**; (upgraded, Leung, 3/4/93).

** 017, 065; 114506, 121146; "Toxicological Testing of HOE 33171 by Repeated Oral Administration to Beagle Dogs for One Year" Brunk et. al., (Hoechst Aktiengesellschaft, Frankfurt, Germany, Report # 84.0437, 7/19/84); 831; HOE 33171 OH ZC94 0001 (94% purity); 0 (cornmeal), 3, 15, and 75 ppm to 6 dogs/sex/dose for 1 year; 1 mid dose male was killed on day 106 due to poor health conditions produced by intestinal stenosis following fatty tissue necrosis; all remaining animals survived the study until scheduled termination; **no adverse effects:** no treatment-related changes in body and organ weights, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, necropsy and histology; normal hepatic and renal functions; NOEL (M/F) $\geq$ 75 ppm (no effect at HDT); study originally reviewed as unacceptable but possibly upgradeable with analysis of test diet to confirm

the actual concentrations of HOE 33171 employed; (Leung, 11/3/92) study was subsequently reviewed with test diet analyses; **acceptable**; (upgraded, Leung, 3/4/93).

ONCOGENICITY, RAT

See Combined, rat

ONCOGENICITY, MOUSE

** 020; 114461; "HOE 33171 - Carcinogenicity Study in Mice (24-month Feeding Study)", Kramer et. al., (Hoechst Aktiengesellschaft, Frankfurt, Germany, Study # 695, 3/11/85); HOE 33171 OH AS 201 (TGAI, 94% purity); 0 (diet), 2.5, 10, and 40 ppm to 50 mice/sex/dose for 24 months; mortalities were reported in all groups during the last 6 months of the study: males 14/50, 21/50, 21/50, 19/50; females 21/50, 30/50, 26/50, 20/50, respectively; no treatment-related changes in body weight, food consumption, hematological parameters, and clinical chemistry; reduced absolute and relative liver weights (85% of control, $p<0.05$) in mid and high dose females without any abnormal histological findings; **no adverse effect;** NOEL (F) = 40 ppm, (M) = 40 ppm (no effect at HDT); **acceptable**; (Leung, 11/6/92).

019; 114459, 114460; "HOE 33171 - Chronic Feeding Study in Mice (Interim Killing after 12 Months)", Kramer et. al., (Hoechst Aktiengesellschaft, Frankfurt, Germany, Study # 695, 11/25/83); HOE 33171 OH AS 201 (TGAI, 94% purity); 0 (diet), 2.5, 10, and 40 ppm to 10 mice/sex/dose for 12 months; **no adverse effects indicated**; all animals survived the study until scheduled termination; no treatment-related changes in clinical signs, body weight, food consumption, hematological parameters, serum biochemistry, macroscopic and histological examinations were detected; dose-related increase in absolute and relative kidney weights in high dose animals was not considered to be toxicologically significant because there was no histological correlation; this increase in kidney weight was only statistically significant in high dose females (108.4% of control, $p<0.05$); HOE 33171 did not induce biosynthesis of hepatic enzymes of foreign substance metabolism or cause peroxisomal proliferation; NOEL (M) $\geq$ 40 ppm (no effect at HDT), (F) = 10 ppm (kidney weight changes only seen at 12 month interim killing but not at terminal killing at 24 months); **supplemental**; (Leung, 11/5/92).

REPRODUCTION, RAT

027; 114478; HOE 33171-Technical Grade: Effects of Dietary Administration upon Reproductive Function in the Rat 1. Dosage Range-Finding Study, J.M. Tesh et al.; Rat; 834; Life Science Research, Essex, England; LSR Report No. 83/HAGO85/376; 2/14/85; HOE 33171 Technical Grade (Code: HOE 33171 OH AS 201), purity: 94.0%; F(0) 6 animals/sex/group; F(1) not mated; Dose (dietary): 0, 40, 160, 320 ppm; Mortality: No deaths for F(0), F(1)-0 (4/69), 40 (0/57), 160 (2/62), 320 (3/45) by day 21 post partum; Observations: no treatment-related signs, no treatment-related effect on body weight gain or food consumption; Necropsy: no treatment-related lesions reported, significant increase in relative liver weight (F(O) males, 320 ppm), in absolute liver weight (F(1) males, 40, 160, 320 ppm), in absolute kidney weight (F(1) males 40, 160, 320 ppm), decrease in absolute thymus weight (F(1) female, 320 ppm); Reproductive factors: no. of implantations, litter size reduced in 320 ppm group, no effect upon mating, fertility index, gestation index; Development: no treatment-effect upon viability index, lactation index, and mean pup weight;

Study **supplemental**. (Moore, 11/5/92)

** 028; 114479; HOE 33171-Technical Grade: Effects upon Reproductive Performance of Rats Treated Continuously Throughout Two Successive Generations, J.M. Tesh et al.; Rat; 834; Life Science Research, Suffolk, England; LSR Report No. 84/HAG087/636, purity: 94.0%; 5/13/85; HOE 33171 Technical Grade (Code: HOE 33171 OH AS 201); 30 animals/sex/group both F0, F1; 2 generations, 2 matings/generation; Dose (dietary): 0, 5, 30, 180 ppm; Mortality: (adults) deaths not treatment-related; Observations: no treatment-related signs or treatment-related effects upon body weight gain or food consumption, both generations; no treatment-related effect upon estrus cycles, pre-coital interval, mating performance, conception rate, gestation length, gestation indices (all matings); no treatment-related effects on live births, viability, sex ratios, development parameters (all matings); Necropsy: no macroscopic lesions adult or offspring; (adults) increased absolute and relative liver weight (M/F:180 ppm), (offspring) increased absolute and relative liver weight (M/F:180 ppm), increased relative kidney weight (M/F:180 ppm), increased absolute and relative thymus weight (M/F:180 ppm); Histopathology: Kidney, increased incidence of nephrocalcinosis in offspring and adult females; Possible target organ: kidney; No adverse effects; Adult NOEL:30 ppm (based on increased liver weight, nephrocalcinosis, 180 ppm); Reproductive NOEL:180 ppm; Developmental NOEL:30 ppm (based on increased kidney and liver, and reduced thymus weight, nephrocalcinosis, 180 ppm); Study acceptable. (Moore, 11/18/92).

029; 114481; Multiple Generation Study on HOE 33171 Substance Technical Grade in Rats, H. Becker et al; 834; Rat; RCC Research and Consulting Company, Itingen, Switzerland; Project No. 034896; 2/20/86; HOE 33171 Technical Grade (Code: HOE 033171 OH ZD97 0001), purity: 97.2%; 30 animals/sex/group, both F0, F1; 2 generations, 2 matings/generation; Dose (dietary): 0, 5, 30, 180 ppm; Mortality: (adults) deaths not treatment related; Observations: (adults) no treatment-related signs or treatment-related effects upon body weight gain or food consumption for both generations; absolute and relative liver and kidney weight increase (M/F:180 ppm); (offspring) mean body weight reduced (180 ppm) 21 days post partum, all matings, increased absolute and relative liver and kidney weights (M/F: 180 ppm); decreased absolute and relative thymus (M/F:180 ppm) and spleen weights (F:180 ppm); Clinical Chemistry: (adults) total lipids reduced (F1, 180 ppm), (offspring) alkaline phosphatase increased (all matings, 180 ppm); Reproductive, Developmental: no treatment-related effect upon estrus cycles, precoital interval, mating performance, conception rate, gestation length, gestation indices, all matings; no treatment-related effects upon live births, viability, sex ratio, developmental parameters for offspring, all matings; Necropsy: no data submitted; Histopathology: no data submitted; NOEL (preliminary): adults-30 ppm (based on significant increase in liver and kidney weights, decrease in thymus weights in 180 ppm group), reproductive: 180 ppm, developmental-30 ppm (based on reduced body weights at 21 days in 180 ppm group); Study unacceptable, may be upgraded with submission of necropsy and histopathology data. (Moore, 11/17/92).

TERATOLOGY, RAT

** 023, 065; 114464, 114465, 121148; "An Oral Embryotoxicity Study of Hoe 33171 O H AT 204 in Wistar Rats" (authors: Drs. Baeder, Weigand, & Kramer); 833; Pharma Research Toxicology, Hoechst, Frankfurt, Germany; report #613/82; 10/4/82; Hoe 33171 O H AT204 (fenoxaprop ethyl); 93.0% purity; administered daily by gavage between gestation days 7-16; doses: 0 (sesame oil), 10, 32, & 100 mg/kg/day; dams sacrificed on day 21; 20 dams/dose; no maternal deaths; slight decrease in maternal food consumption and weight gain compared to controls and appearance of piloerection in several dams at the high dose; 0/60 dams at 0, 10, &

32 mg/kg/day suffered early abortion or fetal death while 4/40 did so at 100 mg/kg/day; high-dose fetuses weighed slightly less than controls (2.97%.20 g vs. 3.34%.37 g, p<.001), were slightly shorter (3.52%.11 cm vs. 3.61%.12 cm, p<.025), displayed weak ossification at 3 sites and anlage of a 14th rib at the 1st lumbar vertebra, and had slight tendencies toward thickened, bent, undulating ribs and fragmented, dysplastic, dislocated, longitudinally displaced, fused sternebrae; reported maternal NOEL=32 mg/kg/day; reported developmental NOEL=32 mg/kg/day; study originally reviewed as unacceptable but possibly upgradeable upon submission of analyses of the dosing solutions; (Rubin, 11/17/92); subsequently rereviewed with dosing solution analyses; **acceptable**; (upgraded, Leung, 3/5/93).

51910-024; 114466; "A Study of the Effect of the Active Ingredient Hoe 033171-Technical on Pregnancy of the Rat" (authors: P. James, R. Billington, R. Clark, & J. Offer); 833; Huntingdon Research Centre, Cambridgeshire, England; report #223/83691; 12/12/83; Hoe 33171 O H ZC96 0002 (fenoxaprop ethyl); 96.2% purity; administered daily by gavage between gestation days 6-15; doses: 0 (sesame oil), 10, 32, & 100 mg/kg/day; 25 dams/dose (24 were pregnant), sacrificed on day 20; no maternal deaths; maternal effects: increased water consumption at 32 & 100 mg/kg/day between days 9-11, decreased weight gain at 100 mg/kg/day between days 6-10, increased liver weight upon sacrifice at 100 mg/kg/day; fetal effects: decreased mean fetal weight at 100 mg/kg/day, increased mean % malformations at 100 mg/kg/day (though not statistically significant), increased mean % visceral anomalies at 32 and 100 mg/kg/day, increased mean % skeletal anomalies at 100 mg/kg/day, increased mean % unossified sternebrae (a type of "variation") at 100 mg/kg/day, and decreased mean % normal sternebrae at 100 mg/kg/day; maternal NOEL=100 mg/kg/day, developmental NOEL=10 mg/kg/day; Study was originally reviewed and found to be **unacceptable but possibly upgradeable** upon submission of analyses of dosing solutions. (Rubin, 11/19/92); study was rereviewed and the developmental NOEL was adjusted to take into account of the dose-related increase in visceral anomalies; status unchanged; (Leung, 2/18/94).

024; 114467; "Embryotoxicity Study in the Rat (Dermal Application)" (Leist, K. H., Research & Consulting Company AG, Itingen, Switzerland, Project # 28765, 10/17/84); 833; HOE 33171 OH ZD96 0001 (96.5% purity); nominal doses of 0 (sesame oil), 100, 300 and 1000 mg/kg/day administered dermally to 25 pregnant female rats/dose for 6 hours/day from days 6 through 15 of gestation; **no adverse effects indicated**; no mortalities were reported; local effects at the application sites consisted of very slight erythema in two to four dams in each of the four dose groups for two to three days; no test article-related differences in the mean number of implantations, resorptions and fetal weight or evidence of embryonic and/or teratogenic potential was detected; nominal maternal and developmental NOEL $\geq$ 1000 mg/kg/day ("limit" test); **unacceptable but possibly upgradeable** with submission of dosing solution analysis to confirm the actual amount of the test article applied dermally; (Leung, 12/11/92).

024; 114468; "Testing for Embryotoxicity and Effects on Postnatal Development in Wistar Rats Following Oral Administration" (Baeder et. al., Hoechst AG, Frankfurt, Germany, Report # 86.0133, 2/4/86); 833; HOE 33171 OH ZD98 0001 (97.9% purity); nominal doses of 0 (sesame oil), 10, 32, and 100 mg/kg administered orally daily to 20 - 22 pregnant/dose on days 7 to 16 of pregnancy; all females allowed to deliver and rear their offsprings for 21-23 days; one low dose animal died during the night after the 8th treatment due to faulty intubation and was replaced; slight reduction in maternal body weight (95.1% of control, $p < 0.05$) accompanied by reduced food consumption (85.5% of control, $p<0.05$) at 100 mg/kg was reversible by the end of the study;

clinical findings included local alopecia and scabbing and piloerection in all three treated groups; **no adverse effects indicated**; no difference between the numbers of live offsprings per litter in the three treated groups as compared with the control group; offsprings in the treated groups were normally developed and their body weights at birth were comparable with those of the control animals; viability of the offsprings in all three dose groups was unimpaired; nominal maternal and developmental NOEL $\geq$ 100 mg/kg/day (no effect at HDT); **unacceptable but possibly upgradeable** with submission of analysis of dosing solutions to confirm the actual dosage administered; (Leung, 12/14/92).

TERATOLOGY, RABBIT

** 025, 065; 114469, 114470, 121148; "An Oral Embryotoxicity Study of HOE 33171 Active Ingredient (Technical Grade) (Code: HOE 33171 OH AT204) in Himalayan Rabbits" (Baeder et. al., Hoechst AG, Frankfurt, Germany, Report #'s 667/82 and 86.0022, 10/21/82); HOE 33171 OH AT 204 (Batch 10750, 93% purity); 833; nominal doses of 0, 12.5, 50, and 200 mg/kg/day in sesame oil to 15 pregnant Himalayan rabbits/dose on the 7th - 19th day of pregnancy; 1 and 2 dams from the low and high dose groups, respectively, were reported dead between the 16th and 19th day of pregnancy; administration of 200 mg/kg to dams led to a decrease in food consumption with a reduction in body weight and increased incidence of abortions; however, on the 20th day of pregnancy when treatment with HOE 33171 was terminated, surviving dams consumed normal quantity of feed with concomitant body weight gain and partial recovery of body weight; fetuses at the high dose exhibited growth retardation, reduced survival rate, diaphragmatic hernias and increased incidence of a 13th rib; **no adverse effects**; maternal and developmental NOEL $\geq$ 50 mg/kg/day (growth retardation, reduced survival rate, increased incidences of abortions and 13th rib); originally reviewed as unacceptable and not upgradeable; lack of dosing solution analyses to confirm the actual dosage administered and all fetuses were not subjected to both visceral and skeletal examinations; (Leung, 11/19/92); subsequently reviewed with dosing solution analyses and additional data from another rabbit teratology study (record #s 114471 and 114472); **acceptable**; (upgraded, Leung, 3/5/93).

** 025, 065; 114471, 114472, 121148; "Testing for Embryotoxicity in Himalayan rabbits Following Oral Administration" (Baeder et. al., Hoechst AG, Frankfurt, Germany, Report #s 83.0516 and 86.0019, 9/29/83); 833; HOE 33171 OH ZC 96 0002 (Serial # 11977, 96.2% purity); 833; nominal doses of 0, 2, 10, and 50 mg/kg/day in sesame oil to 15 pregnant Himalayan rabbits/dose on the 7th - 19th day of pregnancy; Except for one high-dose dam which had died because of vaginal bleeding, all other remaining dams survived the study until scheduled termination; high dose dams exhibited slightly lower food consumption during days 7 - 14, but subsequently returned to normal; delivered fetuses in all dose groups were normally developed and showed no impairment of viability during the first 24 hours; **no adverse effects**; maternal and developmental NOEL $\geq$ 50 mg/kg/day (no effect at HDT); originally reviewed as unacceptable and not upgradeable; lack of dose solution analyses to confirm the actual dosage administered and all fetuses were not subjected to both visceral and skeletal examinations; (Leung, 11/30/92); subsequently reviewed with dosing solution analyses and additional data from another rabbit teratology study (record #s 114469 and 114470); **acceptable**; (upgraded, Leung, 3/5/93).

Summary: Considering both rabbit teratology studies together, the number of fetuses examined for visceral and skeletal abnormalities is adequate.

026; 114473; "Embryotoxicity Study in the Rabbit (Dermal Application)" (Leist, K. H., et. al., Research & Consulting Company AG, Itingen, Switzerland, Project # 28776, 10/3/84); 833; HOE 33171 OH ZD96 0001 (96.5% purity); nominal doses of 0 (sesame oil), 100, 300, and 1000 mg/kg administered dermally 6 hours/day to 16 dams/dose from days 6 through 18 of pregnancy; no mortalities or abnormal clinical findings were reported during this study; erythema, edema, desquamation, exfoliation, and fissuring occurred in all animals and no dose-related differences in intensity of the skin irritations were observed; one dam in the low dose group had only 4 implantation sites and another in the mid dose group had 9 embryonic resorptions on day 28; live fetuses were not found in either dams; no treatment-related differences in reproductive parameters were noted and there was no evidence of embryonic and/or teratogenic potential of the applied test article; **no adverse effects indicated**; nominal maternal and developmental NOEL $\geq$ 1000 mg/kg/day (no effect at HDT); **unacceptable but possibly upgradeable** with submission of dose solution analyses to confirm the actual amounts of test article applied dermally; (Leung, 12/4/92).

TERATOLOGY, MOUSE

026; 114474; "Study of the Effect of the Active Ingredient HOE 33171-Technical on Pregnancy of the Mouse" (James, P. et. al., Huntingdon Research Center PLC., Cambridgeshire, UK, Report # HST 221/222-R/83666, 12/14/83, Re- issued with amended pages on 1/10/85); 833; HOE 33171 OH ZC96 0002 (TGAI); 0 (sesame oil), 2, 10, and 50 mg/kg/day administered orally to 30 dams/dose from days 6 through 15 of pregnancy; no mortalities or treatment-related body weight changes were reported; high dose dams exhibited increased absolute liver weight (125.65% of control, $P<0.01$) with occasional discoloration of the liver; no treatment-related differences in reproductive parameters were noted and there was no evidence of teratogenic potential of the administered test material; **no adverse effects indicated;** nominal maternal and developmental NOEL $\geq$ 50 mg/kg/day (no effect at HDT); study **unacceptable but possibly upgradeable** with submission of dosing solution analysis and dose level justification; (Leung, 12/8/92).

TERATOLOGY, MONKEY

027, 065; 114475, 121151; "Oral Embryotoxicity Study in the Cynomolgus Monkey" (Osterburg, Hazleton Laboratories Deutschland GmbH, Munster, FRG, Project # 169/6, 11/12/84); 833; HOE 33171 OH ZC96 0002 (96.2% purity); 10 and 50 mg/kg/day administered orally to 23 and 11 pregnant Cynomolgus monkeys, respectively, from days 20 through 50 of gestation; **no adverse effects indicated**; 5/21 pregnant animals in the low dose group aborted their fetuses; treatment at the higher dose level resulted in the death of 5/11 pregnant monkeys with 3/11 animals aborting their fetuses; reduced food consumption and diarrhea were observed in all animals during the treatment period; no indication of teratogenic potential; maternal < 10 mg/kg/day (excessive abortions), developmental NOEL $\geq$ 50 mg/kg/day (no effect at HDT); lack of dosing solution analysis to confirm the actual dosage administered and control group; originally reviewed as unacceptable but possibly upgradeable with additional data to eliminate the deficiencies mentioned above; (Leung, 12/9/92). subsequently reviewed with dosing solution analyses and historical control data; **supplemental**; (revised, Leung, 3/5/93).

GENE MUTATION

51910-030; 114482; "Study of the Mutagenic Potential of the Compound Hoe 33171 O H AS201 in Strains of *Salmonella typhimurium* (Ames Test) and *Escherichia coli*"; 842; Dept. of Toxicology, Hoechst AG, Frankfurt/Main, Germany; report #432/82; 8/2/82; Hoe 33171 O H AS201 (fenoxaprop-ethyl); TGAI; *S. typhimurium* strains TA 98, 100, 1535, 1537, & 1538 - assay: reversion to histidine prototrophy; *E. coli* strain WP2 uvrA - assay: reversion to tryptophan prototrophy; dosing (determined by a preliminary cytotoxicity test): 0, 4, 20, 100, 500, 2500, & 5000 ug/plate ± Aroclor 1254-induced S9 rat liver activating microsomes; 48-72 hr @ 37 °C; positive controls demonstrated mutability of all strains; no test article-dependent increase in revertants at any dose, thus, no mutagenic activity; **Acceptable. (Rubin, 11/5/92)

51910-030; 114483; "Test for Mutagenicity in Bacteria Strains in the Absence and Presence of a Liver Preparation" (author: Dr. Engelbart); 842; Arbeitsgruppe Molekularbiologie, Hoechst, Frankfurt, Germany; report #47/79; 7/9/79; Hoe 33171 OH AT 203 (fenoxaprop-ethyl); TGAI; *S. typhimurium strains* TA 98, 100, 1535, & 1537; - assay: reversion to histidine prototrophy; dosing: 0, 4, 20, 100, 500, 1500 (w/o S9 only), & 2500 (+S9 only) ug/plate ± Aroclor 1254-induced S9 rat liver activating microsomes; 48 hr @ 37 °C; no evidence of cytotoxicity; positive controls demonstrated mutability of all strains; no test article-dependent increase in revertants at any dose, thus, no mutagenic activity; **Unacceptable, not upgradeable** (limit dose was not used, no evidence of cytotoxicity at the high dose). (Rubin, 11/6/92)

51910-030; 114484; "Study of the Mutagenic Activity "In Vitro" of the Compound Hoe 33171 OH AS 201 with *Schizosaccharomyces pombe*" (study director: Diego Mellano); 842; Instituto di Ricerche Biomediche, Torino, Italy; study #M 417; 9/10/82; Hoe 33171 OH AS 201 (fenoxaprop-ethyl); 94% purity; *S. pombe* haploid mutant yeast (SP ade 6-60/rad 10-198, h-); dosing (± Aroclor 1254-induced S9 rat liver activating microsomes): 0, 125, 250, 500, 1000 ug/ml; relative survival @ 1000 ug/dose = 51.95% (-S9) and 88.36% (+S9); 4-hr exposure to test article @ 35 °C followed by plating in agar @ 32 °C for 5 days (mutation detected by appearance of white colonies); positive controls demonstrated mutability; no test article-dependent increase in the proportion of white colonies, thus, no mutagenic activity; **Acceptable; (Rubin 11/6/92)

CHROMOSOME EFFECTS

51910-030; 114485; "Study of the Capacity of the Test Article Hoe 33171 OH AS 201 to Induce Chromosome Aberrations in Human Lymphocytes Cultured *In Vitro*" (Study Director: Diego Mellano); 843; Instituto di Ricerche Biomediche, Torino, Italy; study #M 419; 12/23/82; Hoe 33171 OH AS 201 (fenoxaprop-ethyl); 94% purity; lymphocytes freshly isolated from a male volunteer; dosing (± Aroclor 1254-induced S9 rat liver activating microsomes): 0, 1, 10, 100, 1000 ug/ml; 3 hr exposure @ 37 °C; cells arrested at metaphase in colchicine; apprx. 100 metaphases/dose were examined; cytotoxicity evident @ 1000 ug/ml by >80% decline in the # of metaphases; positive controls demonstrated susceptibility to induced chromosome aberrations; no test article dependent increase in chromosome aberrations, thus, no clastogenic activity under the conditions tested; **Acceptable. (Rubin, 11/6/92)

51910-030; 114486; "Micronucleus Test in Male and Female NMR1 Mice Following Oral Administration" (Study Directors: Drs. Leist & Jung); 843; Hoechst Aktiengesellschaft, Frankfurt, Germany; study # 689/81; 9/19/84; Hoe 33171 OH AT 204 (fenoxaprop-ethyl); 93% purity; NMR1 mice; animals dosed twice by gavage, first @ 0 hr, then @ 24 hr, then sacrificed @ 30 hr (6 hr after the second dosing); doses: 0, 18, 180, & 1800 mg/kg; 5/sex/dose; positive controls with

Endoxan (100 mg/kg) demonstrated susceptibility both to induced micronucleus formation in polychromatic cells and to altered polychromatic-to-normochromatic cell ratio; no test article dependent increase in micronucleus formation or change in cell ratio was observed, thus, no clastogenic activity, mitotic spindle disruption, or changes in cell dynamics in the bone marrow occurred under the conditions tested; **Unacceptable** (guidelines require at least 3 time points at the highest dose with none starting earlier than 12 hr after the second application of test article). (Rubin, 11/9/92)

DNA DAMAGE

51910-030; 114487; "Study of the Mutagenic Activity of the Compound Hoe 33171 OH AS 201 with *Saccharomyces cerevisiae*" (Study Director: Diego Mellano); 843; *S. cerevisiae* strain D4; Instituto di Ricerche Biomediche, Torino, Italy; study #M 416; 9/13/82; Hoe 33171 OH AS 201 (fenoxaprop-ethyl); 94% purity; doses (+ Aroclor 1254-induced rat liver S9 activating microsomes): 0, 125, 250, 500, & 1000 ug/ml; 4 hr test article exposure; positive controls: cyclophosphamide (258 ug/mg, +S9 only) and methyl methane sulfonate (84.5 ug/ml, w/o S9 only); experimental incubations contained 2.5% DMSO, positive controls contained no DMSO; mitotic gene conversion either to tryptophan or adenine prototrophy not observed despite evidence for increasing toxicity with dose; **Unacceptable** (positive control data are not comparable to test article data because of disparity in DMSO concentration). (Rubin, 11/9/92)

51910-030; 114488; "Study of the Capacity of the Test Article Hoe 33171 OH AS 201 to Induce "Unscheduled DNA Synthesis" [UDS] in Cultured HeLa Cells" (Study Director: Diego Mellano); 844; Instituto di Ricerche Biomediche, Torino, Italy; study #M 418; 10/10/82; Hoe 33171 OH AS 201 (fenoxaprop-ethyl); 94% purity; doses (+ Aroclor 1254-induced S9 rat liver activating microsomes): 5, 50, & 500 mg/ml; 1 hr test article exposure followed by 3 hr exposure to 1 uCi/ml ^{3}H-thymidine; positive controls: methyl methane sulfonate (1 mM, w/o S9 only) and cyclophosphamide (1.38 mM, +S9 only); UDS assays done in the presence of hydroxyurea (HU=10 mM) to inhibit S-phase DNA synthesis; cytotoxicity test (measured in the absence of HU): high dose of test article inhibited DNA synthesis by 93%, mid-high dose by 31% w/o S9; HU inhibited DNA synthesis in controls by 98% and 97% (+ & - S9); test article did not induce any increase in DNA synthesis in the presence of HU either + or - S9 (positive controls increased synthesis by apprx. 2-fold), thus it apparently does not cause an increase in repair synthesis; **Unacceptable** (positive control data in the presence of HU are too weak to permit interpretation of test article data). (Rubin, 11/10/92)

** 065; 121153; "Unscheduled DNA Synthesis in Hepatocytes of Male Rats In Vitro with HOE 331171 OH ZD 98 0001" (Authors: Miltenburger, H.G., et. al., Cytotest Cell Research Gmbh & Co. KG, Darmstadt, Germany, Test Report Project # CCR 100800, 2/19/87); 844; HOE 33171 OH ZD 98 0001 (Batch # 13982, 96.5% purity); tested in primary Wistar CF HB rat hepatocyte cultures; two separate trials; 6 replicates/dose; concentrations of 0, 1, 3.33, 10, 33.33, and 100 ug/ml; 3 hour exposure to test article and ^{3}H-Tdr; UDS determined by liquid scintillation counting; UDS assay performed in the presence of hydroxyurea (15 mM) to inhibit S-phase DNA synthesis; positive controls functional; **no adverse effect;** test article did not induce DNA repair in the hepatocytes used; **acceptable**; (Leung, 3/8/93).

NEUROTOXICITY

Not required for this compound at this time.